



UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Köster *et al.* Group Art Unit: 1623
Serial No.: 09/484,484 Examiner: Wilson, J.

Filed: January 18, 2000

For: **SOLUTION PHASE BIOPOLYMER SYNTHESIS**

DECLARATION PURSUANT TO 37 C.F.R. §1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, HUBERT KÖSTER, declare as follows:

1. I am a co-inventor of and familiar with the subject matter of the above-captioned application, which was filed on January 18, 2000.
2. I received a Ph.D. in chemistry from Hamburg University, Germany, and did post-graduate research work at the Max Planck Institute for Experimental Medicine in Göttingen, Germany. I was appointed professor of organic chemistry and biochemistry in 1982 at Hamburg University. I hold more than 20 patents and I have authored more than 110 publications.
3. I am a founder of several biotechnology companies, including HK Pharmaceuticals, Inc. I am presently its President and Chief Executive Officer.
4. I and my co-workers have prepared LPCs within the scope of the claims of this application and have tested the LPCs in solution phase biopolymer synthesis (as described in the application).
5. I have reviewed U.S. Patent No. 5,198,540. Provided below is data comparing the yields of oligonucleotide synthesis using LPCs of the instant claims with yields of oligonucleotide synthesis using an LPC of the reference. As shown in the Table below, the yields of oligonucleotide synthesis using LPCs of the instant claims are higher than the yields obtained using the LPCs of the cited reference.

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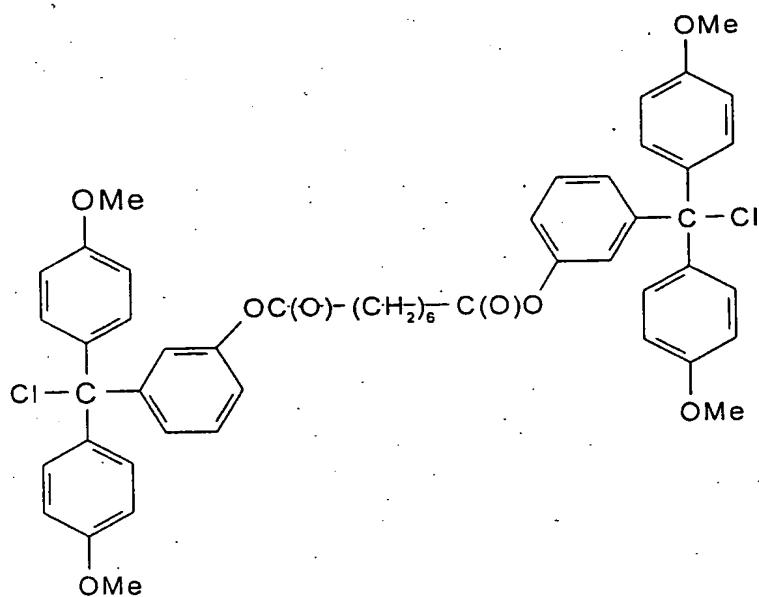
RESULTS

LPCs were synthesized and used in oligonucleotide synthesis according to the exemplified procedures (see, EXAMPLES). Selected results are set forth in Table 1 below.

TABLE 1

| PRODUCT | % YIELD |
|--|---------|
| Oligonucleotide synthesis using an LPC of U.S. Patent No. 5,198,540 ^a | |
| LPC-(TpTpTpA ^{bz} pTp(te)) ₂ ^c | 14 |
| LPC-(TpTpTpA ^{bz} pTpT(Bb)) ₂ ^c | 8 |
| LPC-(TpTpTpA ^{bz} pTpTpC ⁱⁱ p(te)) ₂ ^c | 5 |
| Oligonucleotide synthesis using an LPC of the instant claims ^b | |
| d(5'-O-DMT-G ^{ib} pA ^{bz} pC ^{bz} pG ^{ib} p- G ^{ib} pC ^{bz} pC ^{bz} pA ^{bz} pG ^{ib} pT) ₃ -Aryl-LPC | 33 |

The IPC of the cited reference used in the comparison study was:



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b The LPC of the instant application used in the comparison study was 1,3,5-tris[9-(2'-deoxythymidin-3'-O-yl)-2,5-diaza-1,6,9-trioxononyl]-benzene (dT₃-Aryl-LPC).

c te = 2,2,2-trichloroethyl

bz = benzoyl

tl = 2-toluyl

Bb = 4-tert-butylbenzoyl

ib = isobutyryl

DMT = 4,4'-dimethoxytrityl

p = cyanoethyl-protected phosphate linkage

Materials and Methods

Preparation of 1,3,5-tris[9-(2'-deoxythymidin-3'-O-yl)-2,5-diaza-1,6,9-trioxononyl]-benzene (dT₃-Aryl-LPC)

A. 1,3,5-Benzenetricarboxylic acid tris-N-(2-aminoethyl)amide

1,3,5-Benzenetricarboxylic acid trimethyl ester (1.04 g 4.0 mmol) was treated with ethylenediamine (66.7 ml, 1 mol) in dried methanol at 4 °C. The reaction was complete after 24 h. After lyophilization with dioxane the product was obtained as a white solid; yield: 99 % (1.35 g, 4.0 mmol). ¹H-NMR (400 MHz, d₆-DMSO) δ 1.55 (br, 6 H, -NH₂), 2.72 (m, 6 H, -CH₂NH₂), 3.32 (m, 6 H, -NHCH₂-), 8.42 (s, 3 H, CH_{Ar}), 8.65 (t, 3 H, NH). ¹³C-NMR (100 MHz, d₆-DMSO) δ 42.16 (-CH₂NH₂), 44.16 (-NHCH₂-), 129.30 (CH_{Ar}), 135.95 (C_{Ar}), 166.56 (CO).

B. 1,3,5-Tris-{2,5-diaza-9-[5'-O-(4,4'-dimethoxytriphenylmethyl)-2'-deoxythymidine-3'-O-yl]-1,6,9-trioxononyl}-benzene ((DMT-dT)₃-Aryl-LPC)

A solution of 5'-O-dimethoxytrityl-deoxythymidine-3'-p-nitrophenylsuccinate (approx. 10 mmol) in dioxane/pyridine was concentrated under reduced pressure and dissolved in DMF (25 ml) and pyridine (10 ml). 1,3,5-Benzenetricarboxylic acid tris-N-(2-aminoethyl)amide (673 mg, 2 mmol) was added, the reaction mixture stirred for 16 h at room temperature, concentrated and dissolved in eluent mix. Silica gel column chromatography (step gradient with dichloromethane and 2 to 20% ethanol, 0.5% pyridine, v/v)

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led to mostly pure product fractions. Gel permeation chromatography on Sephadex LH20 (eluent: THF/methanol 80:20 v/v) of the impure fractions gave additional product, total yield: 90 % (4.0 g, 1.8 mmol). ¹H-NMR (400 MHz, CDCl₃) δ 1.32 (s, 9 H, CH₃-, Base), 2.40/2.50 (m, 6 H, H2'), 2.44 (m, 6 H, -COCH₂-), 2.50 (m, 6 H, -CH₂CO-), 3.40 (m, 6 H, H5'), 3.54 (m, 12 H, 2 x -NHCH₂-), 3.77 (s, 18 H, CH₃O-), 4.15 (m, 3 H, H4'), 5.40 (m, 3 H, H3'), 6.32 (dd, 3 H, H1'), 6.8 - 7.4 (m, 39 H, H_{Ar}), 7.60 (s, 3 H, CH, Base), 8.19 (dd, 2 x 3 H, 2 x -NH-CH₂-), 8.40 (s, 3 H, CH_{Ar}). ¹³C-NMR (100 MHz, CDCl₃) δ 11.66 (CH₃, Base), 29.97 (C8), 30.66 (C7), 37.57 (C2'), 39.38 (C4), 40.57(C3), 55.26 (-OCH₃), 63.79 (C5'), 75.80 (C3'), 83.58/84.27 (C1'/C4'), 87.21 (C_z, DMT), 112.06 (C5, Base), 113.34 (C3, DMT), 127.24/128.13/128.23 (C2'/C3'/C4'), DMT), 129.04 (CH_{Ar}), 130.10 (C2, DMT), 134.93 (C6, Base), 135.16 (C1, DMT), 135.27 (C_{Ar}), 144.21 (C1', DMT), 151.34 (C2, Base), 158.79 (C4, DMT), 164.08 (C4, Base), 166.57 (C1), 171.95 (C6), 172.16 (C9).

C. 1,3,5-Tris-[9-(2'-deoxythymidin-3'-O-yl)-2,5-diaza-1,6,9-trioxononyl]-benzene (dT₃-Aryl-LPC)

Procedure 1

Dedimethoxytritylation and solid phase extraction with Fractogel[®] EMD-SO₃ 650 (M) (counterion H⁺), additional purification with gel permeation chromatography using Sephadex LH20: (DMT-dT)₃-Aryl-LPC (1.1 g, 500 μmol) was dissolved in THF/ethanol 99:1 (v/v) and transferred to a column (inner diameter: 30 mm), containing 150 ml ion exchanger, equilibrated with n-hexane/THF/ethanol 60:35:5 (v/v). Dimethoxytrityl-compounds were washed off with n-hexane/THF/ethanol 60:35:5 (v/v, 200 ml), THF/n-hexane/ethanol 60:35:5 (v/v, 200 ml) and THF/ethanol 95:5 (v/v, 200 ml). dT₃-Aryl-LPC was eluted with THF/ethanol 65:35 and THF/ethanol 50:50 (v/v, 300 ml each). The crude product was purified with gel permeation chromatography on Sephadex LH20 (eluent: THF/isopropanol 80:20 v/v), giving a colorless solid after removal of solvents, yield 82% (530 mg, 410 μmol).

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Procedure 2

Dedimethoxytritylation with TFA reagent, purification with solid phase extraction using LiChroprep®-DIOL (Merck): (DMT-T)₃-Aryl-LPC (580 mg, 260 µmol) was dissolved in (10 ml) 1,2-dichloro-ethane/nitromethane/methanol 80:19:1 (v/v) and TFA solution in the same solvent system was added (3%, 7.85 mmol TFA, 20 ml). After 3 minutes the reaction mixture was transferred to a column (inner diameter: 25 mm) filled with LiChroprep®-DIOL (90 ml), equilibrated with dichloromethane/ethanol 95:5 (v/v). The same solvent mixture was used for elution of dimethoxytrityl compounds (300 ml). Washing with dichloromethane/pyridine/ethanol 50:40:10 (v/v) gave the product dT₃-Aryl-LPC after removal of solvents and co-evaporation with toluene (2 x 20 ml) as a colorless crystalline solid, yield: 97 % (330 mg, 252 µmol).

Procedure 3

Dedimethoxytritylation with TFA reagent, purification by gel permeation chromatography using Sephadex LH20 and additional precipitation in diethyl ether: A TFA solution in 1,2-dichloroethane/nitromethane/methanol 80:19:1 (v/v, 2% TFA, 10 mmol) was dropwise mixed with a solution of (DMT-dT)₃-Aryl-LPC (739 mg, 330 µmol) in the same solvent system (5 ml) under stirring at room temperature. After 2 minutes the reaction mixture was cooled in an ice bath and triethylamine (10 mmol in 4 ml of the solvent system) was added. Solvents were removed under reduced pressure and the residue dissolved in N,N-dimethylformamide (5 ml). After chromatography on Sephadex LH20 (eluent: THF/water 70:30, v/v) the most product containing fractions were contaminated with traces of dimethoxytrityl compounds. After removal of the solvents and co-evaporation with dioxane (40 ml), the residue was dissolved in THF/methanol (10 ml) and precipitated into heavily stirred diethyl ether (300 ml). Decantation of the ether layer, filtration of the precipitate under washing with diethyl ether and co-evaporation with pyridine (5 ml) and toluene (2 x 10 ml) gave dT₃-Aryl-LPC as a colorless solid, yield: 88% (380 mg, 290 µmol).

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Procedure 4

Dedimethoxytritylation with TFA reagent and neutralization with trioctylamine, purification by chromatography using NUCLEOPREP 300-30 C₁₈: (DMT-dT)₃-Aryl-LPC (113 mg, 50 μ mol) was dissolved in 1,2-dichloroethane/nitromethane/methanol 80:19:1 (v/v, 4 ml) and a TFA solution in the same solvent system (1.5 mmol TFA in 1 ml) was added dropwise. After 3 minutes the reaction mixture was cooled in an ice bath and neutralized by trioctylamine (1.5 mmol in 1 ml of the solvent system). Solvents were removed under reduced pressure and the residue dissolved in acetonitrile/THF/water 56:14:30 (v/v, 4 ml), also the eluent in the following chromatography using NUCLEOPREP 300-30 C₁₈ (column: 310 x 20 mm, flow 10 ml/min). Product is present in fractions with a retention time between 7 and 9 minutes and well separated of all other components of the probe. After removal of solvents under reduced pressure and lyophilization with dioxane dT₃-Aryl-LPC is obtained as a colorless solid, yield: 98 % (64 mg, 49 μ mol).

Procedure 5

Dedimethoxytritylation with TFA reagent, purification by combined chromatography using NUCLEOPREP 300-30 C₁₈ and Sephadex LH20: (DMT-dT)₃-Aryl-LPC (850 mg, 384 μ mol) was dissolved in 1,2-dichloroethane/nitromethane/methanol 80:19:1 (v/v, 33 ml) and mixed with a TFA solution in the same solvent mixture (11.5 mmol TFA in 10 ml). After 2 minutes a triethylamine solution was added for neutralization under cooling in an ice bath (11.5 mmol, 5 ml in the same solvent system). The reaction mixture was concentrated under reduced pressure and dissolved with the eluent THF/water 60:40 (v/v, 5 ml). Chromatography was performed with a precolumn filled with NUCLEOPREP 300-30 C₁₈ (310 x 20 mm) and a second column with Sephadex LH20 (460 x 30 mm, flow: 1 ml/min). Product containing fractions were combined, concentrated and co-evaporated with dioxane (2 x 40 ml). Final lyophilization with dioxane (10 ml) gave dT₃-Aryl-LPC as a colorless solid, yield: 97% (490 mg, 374 μ mol).

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¹H-NMR (400 MHz, d₆-DMSO) δ 1.78 (s, 9 H, CH₃-, Base), 2.25 (m, 6 H, H2'), 2.40 (m, 6 H, -COCH₂-), 2.55 (m, 6 H, -CH₂CO-), 3.24/3.34 (m, 12 H, 2 x -NHCH₂-), 3.60 (m, 6 H, H5'), 3.97 (m, 3 H, H4'), 5.20 (m, 3 H, H3'), 6.17 (dd, 3 H, H1'), 7.70 (s, 3 H, CH, Base), 8.00 (dd, 3 H, -NHCH₂-), 8.40 (s, 3 H, CH_{Ar}), 8.68 (dd, 3 H, -NHCH₂). ¹³C-NMR (100 MHz, d₆-DMSO) δ 12.19 (CH₃, Base), 29.02 (C8), 29.76 (C7), 36.38 (C2'), 38.18 (C4), 39.13 (C3), 61.26 (C5'), 74.68 (C3'), 83.60/84.47 (C1'/C4'), 109.64 (C5, Base), 128.48 (CH_{Ar}), 134.78 (C_{Ar}), 135.74 (C6, Base), 150.39 (C2, Base), 163.57 (C4, Base), 165.51 (C1), 170.79 (C6), 171.95 (C9).

Synthesis of d(5'-O-DMT-G^{ib}pA^{bz}pC^{bz}pG^{ib}pG^{ib}pC^{bz}pC^{bz}pA^{bz}pG^{ib}pT)₃-Aryl-LPC

The 5'-hydroxyl component dT₃-Aryl-LPC (228 mg 166 μmol) was co-evaporated with dried pyridine (3 x 10 ml) and dissolved in the same solvent (10 ml). (DMT)-dG^{ib}-phosphoramidite (1.0 g, 1.2 mmol) was submitted in a 100 ml-two-necked reaction flask under argon atmosphere. The solution of the 5'-hydroxyl component and tetrazole (6 ml, 30.8 mg/ml in acetonitrile, 2.6 mmol) were dropped in 500 μl portions via syringe through septum to phosphoramidite. In case of incomplete reaction phosphoramidite as solid and tetrazole solution were added (controlled by TLC). After complete reaction the mixture was concentrated under reduced pressure and condensation products isolated by GPC using Sephadex LH20 (eluent: THF/methanol 80:20 v/v, column: 530 x 30 mm, flow: 1 ml/min) without oxidation. Product containing fractions were combined, reduced to a volume of 10 ml and oxidized at 0 °C with t-butylhydroperoxide (80% solution in di-t-butylhydroperoxide, 200 μl, 1.5 mmol) for 5 min. After concentrating and intensive drying in vacuo (5'-O-DMT-G^{ib}pT)₃-Aryl-LPC was obtained as a colorless solid, yield 87% (520 mg, 144 μmol).

The compound was dedimethoxytritylated with TFA reagent, using dichloromethane instead of 1,2-dichloroethane, following the procedure described above. The amounts of used reagents are given in Table 2, the chromatographic conditions were the same. The intermediate d(G^{ib}pT)₃-Aryl-LPC

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was analyzed via MALDI-TOF mass spectrometry ($M + H^+$: theoretical mass 2666.39 Da, found: 2678.3 m/z).

According to the above described cycle, the further elongation steps for the synthesis of $d(5'-O-DMT-G^b pA^{bz} pC^{bz} pG^b pG^b pC^{bz} pC^{bz} pA^{bz} pG^b pT)_3$ -Aryl-LPC were performed, using the amounts of reagents listed in Table 2. Data of analysis of the intermediates via MALDI-TOF mass spectrometry are listed in Table 3. Over all nine cycles the crude compound $d(5'-O-DMT-G^b pA^{bz} pC^{bz} pG^b pC^{bz} pA^{bz} pG^b pT)_3$ -Aryl-LPC was obtained in a yield of 33% (54 μ mol, 750 mg).

Table 2

The amounts of reagents used in the different reaction steps and cycles in solution synthesis of $d(5'-O-DMT-G^b pA^{bz} pC^{bz} pG^b pG^b pC^{bz} pA^{bz} pG^b pT)_3$ -Aryl-LPC

| | 5'-hydroxyl-component: | phosphoramidite: | tetrazole: | t-BuOOH: | yield: | dedimethoxytrityl.:TFA/Et ₃ N | yield: |
|-----------------|---------------------------------------|--|---------------------------------|---------------------------------------|---------------------------------|--|---------------------------------|
| 1.cycle 81 % | 166 μ mol in 10 ml pyridine | 2 g (dG ^b) 2.4 mmol 5 eq. | 12 ml 5.2 mmol 10 eq. | 200 μ l 1.5 mmol 3 eq. | 520 mg 144 μ mol 87 % | 1.14/2.1 ml 15 mmol 30 eq. | 360 mg 135 μ mol 94 % |
| 2.cycle 81 % | 135 μ mol in 10 ml pyridine | 3 g (dA ^{bz}) 3.5 mmol 8.75 equiv. | 18 ml 7.8 mmol 19 equiv. | 200 μ l 1.5 mmol 3.7 equiv. | 630 mg 126 μ mol 93 % | 1.14/2.1 ml 15 mmol 30 equiv. | 450 mg 110 μ mol 87 % |
| 3.cycle 91 % | 110 μ mol in 10 ml pyridine | 1.5g (dC ^{bz}) 1.8 mmol 5.5 equiv. | 12 ml 5.2 mmol 16 equiv. | 200 μ l 1.5 mmol 4.5 equiv. | 630 mg 100 μ mol 91 % | 0.57/1.1 ml 7.5 mmol 23 equiv. | 580 mg 100 μ mol 99 % |
| 4.cycle 84 % | 100 μ mol in 10 ml pyridine | 2. g (dC ^{bz}) 2.4 mmol 8 equiv. | 12 ml 5.2 mmol 17 equiv. | 200 μ l 1.5 mmol 5 equiv. | 750 mg 98 μ mol 98 % | 0.57/1.1 ml 7.5 mmol 25 equiv. | 570 mg 84 μ mol 86 % |
| 5.cycle 95 % | 84 μ mol in 10 ml pyridine | 1.5g (dG ^b) 1.8 mmol 7 equiv. | 9 ml 3.9 mmol 15 equiv. | 200 μ l 1.5 mmol 6 equiv. | 750 mg 83 μ mol 99 % | 0.57/1.1 ml 7.5 mmol 30 equiv. | 650 mg 80 μ mol 96 % |
| 6.cycle 81 % | 80 μ mol in 10 ml pyridine | 1.5g (dG ^b) 1.8 mmol 7.5 equiv. | 9 ml 3.9 mmol 16 equiv. | 200 μ l 1.5 mmol 6 equiv. | 850 mg 80 μ mol 99 % | 0.57/1.1 ml 7.5 mmol 31 equiv. | 620 mg 65 μ mol 81 % |
| 7.cycle 83 % | 65 μ mol in 10 ml pyridine | 2 g (dC ^{bz}) 2.4 mmol 12 equiv. | 1.2 ml 5.2 mmol 26 equiv. | 200 μ l 1.5 mmol 7 equiv. | 770 mg 65 μ mol 99 % | 0.57/1.1 ml 7.5 mmol 38 equiv. | 580 mg 54 μ mol 83 % |
| 8.cycle 99 % | 54 μ mol in 10 ml pyridine | 1.4g (dA ^{bz}) 1.6 mmol 10 equiv. | 9 ml 3.9 mmol 24 equiv. | 200 μ l 1.5 mmol 10 equiv. | 750 mg 54 μ mol 99 % | 0.57/1.1 ml 7.5 mmol 46 equiv. | 660 mg 54 μ mol 99 % |
| 9.cycle | 54 μ mol in 10 ml pyridine | 2 g (dG ^b) 2.4 mmol 15 equiv. | 1.2 ml 5.2 mmol 30 equiv. | 200 μ l 1.5 mmol 10 equiv. | 750 mg 54 μ mol 99 % | - | - |

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In Table 3 the MALDI-TOF mass spectrometry data, achieved from monitoring the complete synthesis are listed. The dedimethoxytritylated intermediates were dissolved in THF/water 70:30 (v/v) and mixed with matrix solution in the same solvent (3-hydroxypicolinic acid, 0.7 mol/l). The 5'-hydroxyl components could be satisfactorily identified up to cycle 6. Deviations from the calculated mass and mass differences are observed at the last three cycles, probably through the increasing occurrence of side products in synthesis and fragmentation during desorption and ionization, leading to signals, which are strongly broadened.

Table 3

Data achieved from 5'-hydroxyl components via MALDI-TOF mass spectrometry.

| intermediates analyzed after dedimethoxytritylation | theoretical mass [Da] | found: M + H ⁺ (m/z) | introduced mass difference |
|---|--------------------------|------------------------------------|--------------------------------------|
| 5'-hydroxyl component in 1. cycle: d(T) ₃ -Aryl-LPC | 1309.26 | 1325.9 | |
| 5'-hydroxyl component in 2. cycle: d(G ^b pT) ₃ -Aryl-LPC | 2666.39 | 2678.3 Δm = 1352 | + (3xdG ^b p) Δm = 1357 |
| 5'-hydroxyl component in 3. cycle: d(A ^b pG ^b pT) ₃ -Aryl-LPC | 4077.49 | 4093.7 Δm = 1415 | + (3xdA ^b p) Δm = 1411 |
| 5'-hydroxyl component in 4. cycle: d(C ^b pA ^b pG ^b pT) ₃ -Aryl-LPC | 5416.54 | 5426.1 Δm = 1332 | + (3xdC ^b p) Δm = 1339 |
| 5'-hydroxyl component in 5. cycle: d(C ^b pC ^b pA ^b pG ^b pT) ₃ -Aryl-LPC | 6755.59 | 6764.6 Δm = 1338 | + (3xdC ^b p) Δm = 1339 |
| 5'-hydroxyl component in 6. cycle: d(G ^b pC ^b pC ^b pA ^b pG ^b pT) ₃ -Aryl-LPC | 8112.83 | 8112.8 Δm = 1366 | + (3xdG ^b p) Δm = 1357 |
| 5'-hydroxyl component in 7. cycle: d(G ^b pG ^b pC ^b pC ^b pA ^b pG ^b pT) ₃ -Aryl-LPC | 9469.11 | 9346.8 Δm = 1234 | + (3xdG ^b p) Δm = 1357 |
| 5'-hydroxyl component in 8. cycle: d(C ^b pG ^b pG ^b pC ^b pC ^b pA ^b pG ^b pT) ₃ -Aryl-LPC | 10808.96 | 10774.8 Δm = 1428 | + (3xdC ^b p) Δm = 1339 |
| 5'-hydroxyl component in 9. cycle: d(A ^b pC ^b pG ^b pG ^b pC ^b pC ^b pA ^b pG ^b pT) ₃ -Aryl-LPC | 12219.97 | 12143.2 Δm = 1368 | + (3xdA ^b p) Δm = 1411 |

* * *

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or

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imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent resulting therefrom.

Date: April 2, 2007.

24743-2301B


Hubert
HUBERT KÖSTER